Locoregional Ablation
Laser ablation for the treatment of patients with primary or metastatic hepatic lesions is considered investigational.

Microwave ablation may be considered medically necessary for the treatment of patients with hepatic lesions for any of the following conditions:

- **Primary hepatocellular carcinoma (HCC)** when all of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Patient is not a candidate for liver transplantation* (see exception below)
  - Presence of three or fewer hepatic lesions
  - Each lesion measures five centimeters (cm) or less in diameter using current technology
  - Absence of extrahepatic metastatic disease
  - All tumor foci can be adequately treated (complete ablation is determined by preoperative imaging)

- **Primary HCC, as a bridge to transplantation*, when all of the following criteria are met**:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Intent is to prevent further tumor growth and to maintain a patient’s candidacy for liver transplant
  - Presence of three or fewer hepatic lesions
  - Each lesion measures five centimeters (cm) or less in diameter using current technology
  - No evidence of extrahepatic spread and/or macrovascular involvement (i.e., portal or hepatic veins)

  **Note**: Criteria for ablative therapies as a bridge to transplantation are generally consistent with the United Network for Organ Sharing (UNOS) policy on Organ Distribution: Liver Transplant Candidates with Hepatocellular Carcinoma (HCC); Section 3.6.4.4 (11/9/2010).

- **Hepatic metastases from colorectal cancer** when all of the following criteria are met:
  - Patient is not a candidate for curative hepatic surgical resections due to limited hepatic reserve and/or comorbid conditions and/or the location (e.g., adjacent to a major vein) or number of lesions
  - Presence of four to five or fewer hepatic lesions
  - Each lesion measures five centimeters (cm) or less in diameter using current technology
  - Absence of extrahepatic metastatic disease
  - All tumor foci can be adequately treated (complete ablation determined by preoperative imaging)

- **Hepatic metastases from neuroendocrine tumors** when all of the following criteria are met:
  - Patient has symptomatic disease (e.g., wheezing, flushing of the skin, abdominal cramps, diarrhea, heart disease)
  - Systemic therapy has failed to control symptoms (e.g., Octreotide therapy)
Microwave ablation for primary HCC or hepatic metastases is considered investigational for the treatment of any of the following:

- Primary HCC when there are either of the following:
  - More than three hepatic lesions nodules
  - When not all sites of tumor foci can be adequately treated
- Primary HCC when used to downstage (downsize) HCC in patients being considered for liver transplant
- Hepatic metastasis from colorectal cancer or neuroendocrine tumors not meeting the medically necessary criteria above
- Hepatic metastases from other types of cancer with the exception of colorectal or neuroendocrine cancer tumors

**Policy Guidelines**

Downstaging (downsizing) therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) that are beyond the accepted transplant criteria.

**Neuroendocrine Tumors**

Neuroendocrine tumors (NETs) may be referred to by their anatomical location (e.g., pulmonary neuroendocrine tumor, gastroenteropancreatic neuroendocrine tumor). Neuroendocrine tumors include the following:

- Carcinoid tumors
- Islet cell tumors (or pancreatic endocrine tumors)
- Neuroendocrine unknown primary
- Adrenal gland tumors
- Pheochromocytoma/paraganglioma
- Poorly differentiated (high grade or anaplastic)/small cell
- Multiple endocrine neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple endocrine neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Symptomatic disease from neuroendocrine tumors may include hot, red flushing of the face, severe and debilitating diarrhea, asthma attacks, palpitations, low blood pressure, fatigue, dizziness, and weakness. Extreme symptoms may include heart disease, bronchial constriction, and bowel obstruction.

Systemic therapies for neuroendocrine tumors vary depending on the location and characteristics. Therapies may include, but are not limited to: octreotide, interferon, cytotoxic chemotherapy, angiogenesis inhibitors, and epidermal growth factor inhibitors.

**Coding**

There are no CPT codes specific to microwave ablation. The following CPT codes would likely be used:

- 19499: Unlisted procedure, breast
- 32998: Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; radiofrequency
Microwave and Locoregional Laser Tumor Ablation

• 47370: Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
• 47380: Ablation, open, of one or more liver tumor(s); radiofrequency
• 47382: Ablation, one or more liver tumor(s), percutaneous, radiofrequency
• 50592: Ablation, one or more renal tumor(s), percutaneous, unilateral, radiofrequency

Note: According to an American Medical Association (AMA) publication (Clinical Examples in Radiology, Vol. 8, Issue 3; Summer 2012), “microwave is part of the radiofrequency spectrum, and simply uses a different part of the radiofrequency spectrum to develop heat energy to destroy abnormal tissue.” Therefore, the American Medical Association recommends that microwave ablation be reported using CPT codes for radiofrequency ablation: 32998 (pulmonary), 47382 (liver), and 50592 (renal).

If there is no specific CPT code for ablation, the unlisted CPT code for the anatomic area should be reported, such as code 60699 for unlisted procedure, endocrine system (for adrenal or thyroid ablation).

CPT code 76940 would be used to describe the ultrasound guidance for, and monitoring of, parenchymal tissue ablation.

Description

Microwave ablation (MWA) is a technique to destroy tumors and soft tissue using microwave energy to create thermal coagulation and localized tissue necrosis. MWA is used to treat tumors not amenable to resection and to treat patient’s ineligible for surgery due to age, comorbidities, or poor general health. MWA may be performed as an open procedure, laparoscopically, percutaneously, or thoracoscopically under image guidance (e.g., ultrasound, computed tomography, magnetic resonance imaging) with sedation, or local or general anesthesia. This technique is also referred to as microwave coagulation therapy.

Related Policies

• Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors
• Cryosurgical Ablation of Primary or Metastatic Liver Tumors
• Radioembolization for Primary and Metastatic Tumors of the Liver
• Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
• Radiofrequency Ablation of Primary of Metastatic Liver Tumors
• Transcatheter Arterial Chemoembolization to Treat Primary or Metastatic Liver Malignancies

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Several devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for MWA. Covidien’s (now Medtronic’s) Evident™ Microwave Ablation System was cleared for marketing through the 510(k) process for soft tissue ablation, including partial or complete ablation of nonresectable liver tumors. The following devices have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical’s (now Perseon) MicroThermX® Microwave Ablation System (MTX-180)
- Valleylab’s (subsidiary of Covidien) VivaWave® Microwave Ablation System
- Vivant’s (now Valleylab in 2005) Tri-Loop™ Microwave Ablation Probe
- MicroSurgeon’s Microwave Soft Tissue Ablation System
- Microsulis Medical’s (now AngioDynamics) Acculis® Accu2i
- NeuWave Medical’s Certus® 140

The Food and Drug Administration determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. Food and Drug Administration product code: NEY.

This evidence review does not address MWA for the treatment of splenomegaly or ulcers or as a surgical coagulation tool.

Rationale

Background

Microwave Ablation

Microwave ablation (MWA) uses microwave energy to induce an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field, which causes water molecule rotation and creates heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, 2- to 3-cm elliptical area (5×3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2 to 3 antennas may be used simultaneously to increase the targeted area of MWA and shorten the operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within 1 minute after a pulse of energy, and multiple pulses may be delivered within a treatment session, depending on tumor size. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is a local recurrence, it occurs at the margins. Treatment may be repeated as needed. MWA may be used for the following purposes: (1) to control local tumor growth and prevent recurrence; (2) to palliate symptoms; and (3) to prolong survival.

MWA is similar to radiofrequency (RFA) and cryosurgical ablation. However, MWA has potential advantages over RFA and cryosurgical ablation. In MWA, the heating process is active, which produces higher temperatures than the passive heating of RFA and should allow for more complete thermal ablation in less time. The higher temperatures reached with MWA (>100°C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels, potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating and, therefore, does not flow electrical current through patients and does not require grounding pads, because there is no risk of skin burns. Additionally, MWA does not produce electric noise, which allows ultrasound guidance during the procedure without interference, unlike RFA. Finally, MWA can take less time than RFA, because multiple antennas can be used simultaneously.

Adverse Events

Complications from MWA are usually mild and may include pain and fever. Other complications associated with MWA include those caused by heat damage to normal tissue adjacent to the
tumor (eg, intestinal damage during MWA of the kidney or liver), structural damage along the probe track (eg, pneumothorax as a consequence of procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury, or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant women because potential risks to the patient and/or fetus have not been established, and in patients with implanted electronic devices (e.g., implantable pacemakers) that may be adversely affected by microwave power output.

Applications
MWA was first used percutaneously in 1986 as an adjunct to liver biopsy. Since then, MWA has been used to ablate tumors and tissue to treat many conditions including hepatocellular carcinoma, breast cancer, colorectal cancer metastatic to the liver, renal cell carcinoma, renal hamartoma, adrenal malignant carcinoma, non-small-cell lung cancer, intrahepatic primary cholangiocarcinoma, secondary splenomegaly and hypersplenism, abdominal tumors, and other tumors not amenable to resection. Well-established local or systemic treatment alternatives are available for each of these malignancies. The potential advantages of MWA for these cancers include improved local control and other advantages common to any minimally invasive procedure (e.g., preserving normal organ tissue, decreasing morbidity, shortening length of hospitalization). MWA also has been investigated as a treatment for unresectable hepatic tumors, as both primary and palliative treatment, and as a bridge to liver transplant. In the latter setting, MWA is being assessed to determine whether it can reduce the incidence of tumor progression while awaiting transplantation and thus maintain a patient’s candidacy while awaiting a liver transplant.

Hepatic Tumors
Hepatic tumors can arise either as primary liver cancer (HCC) or by metastasis to the liver from other primary cancer sites. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential. Partial liver resection, hepatectomy, is considered the criterion standard. However, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Various locoregional therapies for unresectable liver tumors have been investigated including: microwave coagulation, RFA, cryosurgical ablation (cryosurgery), laser ablation, transhepatic artery embolization/chemoembolization (TACE), percutaneous ethanol injection, and radioembolization (Yttrium-90 microspheres).

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be
adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Unresectable Primary or Metastatic Solid Tumor**

**Clinical Context and Therapy Purpose**

The purpose of microwave ablation (MWA) in patients who have unresectable primary or metastatic solid tumors (e.g., breast, primary and metastatic hepatic, pulmonary, or renal tumors) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of MWA improve the net health outcome in individuals with unresectable primary or metastatic solid tumors?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant populations of interest are those with unresectable primary or metastatic solid tumors such as breast, primary or metastatic hepatic, pulmonary, or renal cancer.

**Interventions**

The therapy being considered is MWA.

**Comparators**

The following therapies are currently being used to make decisions about managing unresectable primary or metastatic solid tumors: radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and cryoablation.

**Outcomes**

The general outcomes of interest are overall survival, tumor recurrence rates, complete ablation, and pain. Treatment-related morbidities may vary by tumor type. For example, treatment for lung cancer may lead to pneumothorax.

**Timing**

Follow-up for treatment-related morbidity is months postprocedure. Follow-up to monitor for overall survival and recurrence rates may be measured in years of follow-up.

**Setting**

Typically, MWA is performed under conscious sedation in an outpatient setting.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Breast Cancer Systematic Reviews**

A systematic review by Zhao and Wu (2010) assessing ablation techniques for breast cancer found that only 0% to 8% of breast cancer tumors were completely ablated with MWA. The studies identified by reviewers were mostly feasibility and pilot studies conducted in research settings.
**Prospective Studies**

Zhou et al (2012) reported on 41 patients treated with MWA directly followed by mastectomy for single breast tumors with a mean volume of 5.26 cm (range, 0.09-14.14 cm). Complete tumor ablation was found by microscopic evaluation in 37 (90%) of the 41 tumors ablated (95% confidence interval [CI], 76.9% to 97.3%). Reversible thermal injuries to the skin and pectoralis major muscle occurred in 3 patients.

**Hepatocellular Carcinoma**

**Systematic Reviews**

Chinnaratha et al (2016) published a systematic review of RCTs and observational studies that compared the effectiveness and safety of RFA with MWA in patients who had primary HCC. MEDLINE, EMBASE, and Cochrane Central databases were searched between 1980 and 2014 for human studies comparing the 2 technologies. The primary outcome was the risk of local tumor progression (LTP); secondary outcomes were complete ablation, overall survival (OS), and major adverse events. Odds ratios were combined across studies using a random-effects model. Ten studies (2 prospective, 8 retrospective) were included. The overall LTP rate was 14% (176/1298). There was no difference in LTP rates between RFA and MWA (odds ratio, 1.01; 95% CI, 0.67 to 1.50; p=0.9). The complete ablation rate, 1- and 3-year OS, and major adverse events were similar between the 2 modalities (p>0.05 for all). Subgroup analysis showed LTP rates were lower with MWA for treatment of larger tumors (odds ratio, 1.88; 95% CI, 1.10 to 3.23; p=0.02). No significant publication bias was detected nor was interstudy heterogeneity (I²<50%, p>0.1) observed for any measured outcomes.

Bertot et al (2011) conducted a systematic review of ablation techniques for primary and secondary liver tumors. Reviewers selected 2 studies using MWA (total N=1185 patients). Pooled analysis was performed using a random-effects model because of significant study heterogeneity. The pooled mortality rate for MWA was 0.23% (95% CI, 0.0% to 0.58%). The pooled rate of major complications following MWA was 4.6%.

Ong et al (2009) conducted a systematic review of studies on MWA for primary and secondary liver tumors. Results pooled from 25 clinical studies suggested MWA is an effective and safe technique for liver tumor ablation and has low complication rates and OS rates comparable to hepatic resection. However, rates of local recurrence after MWA were higher than hepatic resection. In most studies, mean HCC recurrence rates were approximately 10% but were as high as 50% in some studies. OS rates for HCC were as high as 92% at 3 years and 72% at 5 years, comparable to OS rates for RFA and percutaneous ethanol injections. Pain and fever were the most frequently reported complications, which increased with more tumors, larger tumors, and number of microwave antennas used.

**Randomized Controlled Trials**

Taniai et al (2006) reported on 30 patients with multiple HCC tumors who underwent reduction hepatectomy with postoperative TACE. Before surgery, patients were randomized to no intraoperative adjuvant therapy (n=15) or intraoperative adjuvant therapy with MWA (n=10) or RFA (n=5) of satellite lesions. No significant differences were identified between the no intraoperative adjuvant therapy and intraoperative adjuvant therapy groups, including sex, age, nodule size (maximum tumor size, 4.3 cm vs 3.8 cm, respectively), Child-Pugh cirrhosis class, and number of nodules. Cumulative survival rates at 3 and 5 years did not differ significantly between the no intraoperative adjuvant therapy group (35.0% and 0%, respectively) and the intraoperative adjuvant therapy group (35.7% and 7.7%, respectively). The α-fetoprotein level, number of tumors, maximum tumor size, and clinical stage, but not intraoperative adjuvant therapy, were identified as independent prognostic survival factors.

Shibata et al (2002) reported on 72 consecutive patients with 94 small HCC nodules randomized by sealed envelope to MWA or RFA performed by a single surgeon. No significant differences were identified between treatment group characteristics (e.g., sex, age, nodule size, Child-Pugh...
class, number of nodules). In the RFA group, complete ablation was seen in 46 (96%) of 48 nodules (mean size, 2.3 cm; range, 1.0-3.7 cm) and 41 (89%) of 46 nodules (mean size, 2.2 cm; range, 0.9-3.4 cm) treated with MWA (p=0.26). Treatment outcomes did not differ significantly between groups in rates of untreated disease during the 6- to 27-month follow-up (8/46 nodules for MWA vs 4/48 nodules for RFA), or major complication rates (4 vs 1, respectively). Major complications included 1 case of segmental hepatic infarction in the RFA group compared with 1 case of each of the following in the MWA group: liver abscess, cholangitis with intrahepatic bile duct dilatation, subcutaneous abscess with skin burn, and subcapsular hematoma. Life-threatening complications were not reported. The number of treatment sessions required per nodule in the RFA group (1.1) was significantly lower than in the percutaneous MWA group (2.4; p<0.001).

**Comparative Studies**
The available studies are nonrandomized comparisons, except a retrospective study.

Abdelaziz et al (2015) reported on a prospective study that evaluated the efficacy and safety of MWA and TACE for large tumors (5-7 cm) and assessed their effects on LTP and survival. Sixty-four patients with large lesions were divided into 2 groups treated by MWA or by TACE. Both groups were comparable in demographic and ultrasonographic tumor features. MWA completely ablated 75% of cases in fewer sessions than TACE, with a lower incidence of tumor recurrence (p=0.02), development of de novo lesions (p=0.03), and occurrence of posttreatment ascites (p=0.003). MWA also had higher OS rates (p=0.04) than TACE. Mean OS in the MWA group was 22 months and 14 months in the TACE group. Actuarial probabilities of survival at 12 and 18 months were 78% and 68%, respectively, in the MWA group and 52% and 29%, respectively, in the TACE group.

Vogl et al (2015) conducted a retrospective comparative study that enrolled 53 patients with 68 liver lesions due to HCC. MWA was performed in 36 patients and RFA in 32 patients. There were no differences between groups for complete response immediately following treatment or for progression-free survival at 12 months or OS at 3 years.

Ding et al (2013) retrospectively compared 113 patients treated with MWA for 131 HCC tumors and 85 patients treated with RFA for 98 HCC tumors. Rates of complete ablation, local recurrence, disease-free survival (DFS), and cumulative survival (at 1, 2, 3, and 4 years), and major complications did not differ significantly between groups.

In another study, Ding et al (2013) retrospectively compared complications for 556 patients treated with MWA for 1090 liver tumors (491 HCC, 18 cholangiocarcinoma, 47 liver metastases) and 323 patients treated with RFA for 562 liver tumors (279 HCC, 6 cholangiocarcinoma, 38 liver metastases). Rates of death (2/556 MWA, 1/323 RFA patients), as well as major and minor complications, did not differ significantly between groups.

Takami et al (2013) reported on 719 patients treated with MWA for HCC (mean tumor size, 2.7 cm) at a single institution. OS rates were 97.7% at 1 year, 62.1% at 5 years, and 34.1% at 10 years. For 390 patients with 3 or fewer tumors measuring 3 cm or less, OS rates were 97.9% at 1 year, 70.0% at 5 years, and 43.0% at 10 years. When MWA results were compared with 34 patients treated at the same institution with hepatic resection, OS, DFS, and local recurrence rates did not differ significantly.

In a single-center report on needle track seeding, Yu et al (2012) followed 1462 patients treated with MWA for 2530 liver tumors over a 14-year period. Twelve seeding nodules with a mean size of 2.3 cm (range, 1.3-3.9 cm) were found in 11 patients within 6 to 37 months (median, 10 months) after receiving MWA.
Case Series
Zhou et al (2011) prospectively evaluated MWA in 215 patients with HCC tumors of 6 cm or less in size (median size, 2.9 cm) in a single-center, phase 2 study. Technical effectiveness was reported in all patients. OS rates at 1, 2, 3, 4, and 5 years were 94%, 82.9%, 66%, 54.1%, and 44.4%, respectively, and median OS time was 40 months (range, 4-106 months). Complications related to the procedure included 3 cases of pleural effusion and a case of bile duct injury.

In another prospective study by Zhou et al (2009), MWA was performed on 124 patients with 144 HCC lesions and 28 patients with 35 hepatic metastases. Included in the 152 subjects were 59 patients with 61 lesions (mean size, 2.7 cm) located less than 0.5 cm from the gastrointestinal tract and 93 patients with 126 lesions (mean size, 2.4 cm) located more than 0.5 cm from the gastrointestinal tract. No procedural complications were noted, though tumor seeding occurred in 3 patients. Complete ablation was achieved in 47 (88.7%) of 53 lesions in the group with tumors near the GI tract and 116 (92.1%) of the other 126 lesions, as confirmed by imaging during the 3- to 32-month follow-up. LTP occurred in 16 tumors by 9 months. Separate treatment outcomes for HCC tumors and hepatic metastasis were not provided.

Lu et al (2005) reported on a retrospective comparison of 102 patients with HCC treated with MWA (49 patients with 98 nodules; mean size, 2.5 cm) or RFA (53 patients with 72 nodules; mean size, 2.6 cm). Patient follow-up was about 25 months in both groups. Complete ablation did not differ significantly between groups (95% [93/98] tumors in the MWA group vs 93% [67/72] tumors in the RFA group). However, complete ablation rates improved for smaller tumors of less than 3 cm in size to 98.6% (73/74) in the MWA group and 98% (50/51) in the RFA group. In tumors larger than 3 cm, complete ablation rates declined to 83.3% (20/24) in the MWA group and 81% (17/21) in the RFA group. There were also no significant differences between groups in rates of local tumor recurrence (11.8% for MWA vs 20.9% for RFA), major complications (8.2% vs 5.7%, respectively), or DFS at 1, 2, and 3 years (45.9%, 26.9%, and 26.9% vs 37.2%, 20.7%, and 15.5%, respectively).

Hepatic Metastases from Primary Cancers from Other Sites
Systematic Reviews
A Health Technology Assessment by Loveman et al (2014) and a Cochrane review by Bala et al (2013) reported on ablation for liver metastasis. Reviewers found insufficient evidence to determine any benefits of MWA for liver metastasis over surgical resection.

In Bertot’s 2011 systematic review (previously described), only 1 RCT was identified comparing MWA for hepatic metastases with the criterion standard of surgical resection.

Pathak et al (2011) conducted a systematic review of ablation techniques for colorectal liver metastases, which included 13 studies on MWA (total N=406 patients) with a minimum of 1-year follow-up. Mean survival rates were 73%, 30%, and 16% and ranged from 40% to 91.4%, 0% to 57% and 14% to 32% at the 1-, 3-, and 5-year follow-ups, respectively. Minor and major complication rates were considered acceptable, and ranged from 6.7% to 90.5% and 0% to 19% respectively. Local recurrence rates ranged from 2% to 14%.

In the systematic review by Ong (2009), previously described, local recurrence rates for liver metastases after MWA treatment averaged 15% but varied between 0% and 50% in the 7 studies that addressed liver metastases.

Randomized Controlled Trials
Shibata et al (2000) reported on 30 patients with hepatic metastases from colorectal cancer randomized without stratification to MWA after laparotomy (n=14) or to hepatectomy (n=16). Of the original 40 patients, 10 patients were excluded because researchers discovered intraoperatively that they did not meet study criteria (they had extensive metastasis or ≥10 tumors). The 2 treatment groups did not differ significantly in age (mean age, 61 years in both groups), number of tumors (mean, 4.1 vs 3.0, respectively), or tumor size (mean, 2.7 cm vs 3.4 cm,
respectively). No significant differences were observed in survival (27 months for MWA vs 25 months for hepatectomy) or mean DFS (11.3 months for MWA vs 13.3 months for hepatectomy). Complications in the MWA group included 1 hepatic abscess and 1 bile duct fistula. In the hepatectomy group, complications were 1 intestinal obstruction, 1 bile duct fistula, and wound infection.

**Nonrandomized Trials**

Liu et al (2013) reported on liver metastases for 35 patients treated with MWA (62 tumors) and 54 patients treated with RFA (70 tumors). Ablation was complete in 89% (117/132) of tumors and did not differ significantly between tumor types: 86% (56/65) for metastatic colorectal cancer and 91% (61/67) for other metastatic diseases. Tumors 3.0 cm or smaller were completely ablated significantly more often than tumors larger than 3.0 cm (94% vs 67%, p=0.001).

Lorentzen et al (2011) retrospectively reviewed use of MWA in 39 patients with 125 liver metastases from the primary sites of colorectal cancer (n=31), breast cancer (n=6), carcinoid tumor (n=1), and gastrointestinal stromal tumor (n=1). Complete ablation was achieved in 100% of tumors (median size, 1.5 cm) with 1 treatment session in 34 patients, in 2 sessions for 4 patients, and in 3 sessions for 1 patient. One case of a liver abscess, which resolved after percutaneous drainage, was the only major complication reported. Four minor complications were reported (1 incidence of ascites, 3 complaints of puncture site pain). At a median follow-up of 11 months, LTP was seen in 12 (10%) of 125 tumors in 10 (26%) of the 39 patients.

In a prospective, single-institution, phase 2 study, Martin et al (2010) reported on 100 patients treated with 270 open or MWA for HCC (n=17) and liver metastases from the primary sites of colorectal (n=50), carcinoid (n=11), and other cancers (n=22, including cholangiocarcinoma, metastatic breast, renal cell carcinoma, bladder, carcinoid, melanoma, and sarcoma). Median tumor size was 3.0 cm. Thirty-eight patients received MWA, 53 patients had MWA plus concomitant hepatic resection, and 9 patients had MWA concomitant with other organ resection. Only 2 patients had incomplete ablations after the procedure. No bleeding complications were experienced, but 2 cases of hepatic abscess and 2 cases of hepatic insufficiency occurred. At a median follow-up of 36 months, 5 patients had incomplete ablations, and 2 (2%) patients had local tumor recurrence; 37 (37%) patients developed recurrence at nonablated sites.

**Lung Cancer**

Acksteiner and Steinke (2015) reported on a retrospective study that evaluated the safety, effectiveness, and follow-up imaging of MWA in 10 patients (age range, >75 years) with early-stage non-small-cell lung cancer. Follow-up with computed tomography and fluorine 18 fluorodeoxyglucose-positron emission tomography extended for up to 30 months (median, 12 months). No periprocedural deaths or major complications were reported. Three patients showed growth of the treated lesions, 1 patient died (age 90) due to unknown causes. One patient still living presented with local progression and disseminated metastatic disease at 12 months. One patient showed increasing soft tissue mass at the ablation site 15 months posttreatment, but 3 consecutive core biopsies over 2 months failed to confirm tumor recurrence.

An observational study by Sun et al (2015) evaluated the clinical efficacy and utility of percutaneous MWA therapy for lung cancer without surgical treatment. Thirty-nine lesions in 29 patients with peripheral lung cancer were treated by percutaneous MWA therapy under local anesthesia. Treatments were completed in 29 patients. Eight, 14, 4, and 3 patients, respectively, achieved complete remission, partial remission, stable status, and progression for an effectiveness rate of 76%. Complications included 5, 2, and 15 cases of pneumothorax, pleural effusion, and fever, respectively. No complications from needle track insertion were observed. Mean progression-free survival was 15 months. One- and 2-year OS rates were 91% and 83%, respectively.
Belfiore et al (2013) retrospectively reviewed data on 56 patients treated with MWA for inoperable lung cancer or metastatic pulmonary metastases. DFS rates were 69% at 1 year, 54% at 2 years, and 49% at 3 years. Pneumothorax was reported in 18 (32%) patients.

Lu et al (2012) retrospectively reviewed 69 patients treated with MWA for inoperable lung cancer or metastatic pulmonary metastases. OS rates for patients with pulmonary metastases at 1, 2, and 3 years were 48%, 24%, and 14%, respectively. The recurrence-free survival rates for patients with non-small-cell lung cancer at 1, 2, and 3 years were 73%, 50%, and 27%, respectively. OS rates for all patients were 67% at 1, 45% at 2, and 25% at 3 years. Pneumothorax was reported in 25% of patients.

Vogl et al (2011) prospectively assessed 80 patients treated with MWA for inoperable pulmonary metastases. Rates were 91% at 1 year and 75% at 2 years. Pneumothorax occurred in 11 (9%) of 130 MWA sessions, and pulmonary hemorrhage occurred in 8 (6%) of 130 sessions.

Primary Renal Tumors
Systematic Reviews
In a systematic review and meta-analysis, Katsanos et al (2014) compared thermal ablation (MWA and RFA) with surgical nephrectomy for small renal tumors (mean size, 2.5 cm). The analysis included 1 randomized study on MWA (described below) and 5 cohort studies on RFA (total N=587 patients). In the ablation group, complication rates and renal function declines were significantly more than in the nephrectomy group (p=0.04 and p=0.03, respectively). The local recurrence rate was 3.6% in both groups (relative risk, 0.92; 95% CI, 0.4 to 2.14; p=0.79) and DFS up to 5 years did not differ significantly between groups (hazard ratio, 1.04; 95% CI, 0.48 to 2.24; p=0.92).

Martin et al (2013) conducted a meta-analysis comparing MWA with cryoablation for small renal tumors. The analysis included 7 MWA studies (n=164 patients) and 44 cryoablation studies (n=2989 patients). Selected studies were prospective or retrospective, nonrandomized, noncomparative studies. Mean follow-up duration was shorter for MWA (17.86 months) than for cryoablation (30.22 months; p=0.07). Mean tumor size was significantly larger in the MWA studies than in the cryoablation studies (2.58 cm vs 3.13 cm, respectively; p=0.04). LTP (4.07% vs 2.53%, respectively; p=0.46) and progression to metastatic disease (0.8% vs 0%, respectively; p=0.12) did not differ significantly.

Randomized Controlled Trials
Guan et al (2012) reported on a prospective randomized study that compared the use of MWA with partial nephrectomy (the criterion standard of nephron-sparing surgical resection) for solitary renal tumors less than 4 cm. Forty-eight patients received MWA and 54 had partial nephrectomy. Patients in the MWA group (6 [23.5%]) had significantly fewer postoperative complications than in the partial nephrectomy group (18 [33.3%]; p=0.019). MWA patients also had significantly less postoperative renal function declines (p=0.009) and estimated perioperative blood loss (p<0.001) than partial nephrectomy patients. At last follow-up, estimated glomerular filtration rate declines in both groups were similar (p=1.00). Disease-specific deaths did not occur, and overall local recurrence-free survival by Kaplan-Meier estimates at 3 years was 91.3% for MWA and 96.0% for partial nephrectomy (p=0.541).

Case Series
Yu et al (2012) reported on a retrospective review of 46 patients treated with MWA for renal cell carcinoma. Complete ablation occurred in 98% (48/49) of tumors (mean tumor size, 3.0 cm). At a median follow-up of 20.1 months, all 46 patients were metastasis-free. OS rates were 100% at 1 and 2 years and 97.8% at 3 years.

Muto et al (2011) reported on complete tumor coagulation necrosis in 10 patients treated with MWA for clear cell renal carcinoma (median tumor size, 2.75 cm). No complications were reported during or after the procedure. Bai et al (2010) reported complete laparoscopic MWA in...
17 of 18 clear cell renal carcinoma tumors (mean tumor size, 2.8 cm). In this study, evidence of disease progression was not found at a median follow-up of 20 months. Complications reported were mild (18.2%), and renal function did not significantly deteriorate.

In a study of 10 patients with solid-enhancing renal tumors (median size, 3.65 cm) who were treated with MWA, Castle et al (2011) reported tumor recurrence in 3 of 8 tumors at a mean follow-up of 17.9 months. Twenty percent of patients experienced intraoperative complications while 40% experienced postoperative complications, including perinephric hematoma, splenic capsular tear, pleuritic chest pain, skin burn, fever, hematuria, genitofemoral neuralgia, and urinoma.

In another study, Guan et al (2010) reported on the safety of MWA for renal hemangioma. In this case series, 15 of 16 patients had complete tumor ablation. Disease recurrence was not reported at a median follow-up of 16 months.

Other Tumors or Conditions
No RCTs on the use of MWA for other tumors or conditions have been identified. A systematic review of ablation therapies, including MWA, for locally advanced pancreatic cancer was published by Keane et al (2014). Reviewers found limited evidence on the use of MWA for pancreatic cancer.

Case studies and retrospective reviews on the use of MWA for adrenal carcinoma, metastatic bone tumors, intrahepatic primary cholangiocarcinoma, benign thyroid tumors, and other nononcologic conditions (i.e., bleeding peptic ulcers, esophageal varices, secondary hypersplenism) were identified.

Locoregional Ablative Therapies
There is research available for each of the ablative therapies. However, many of the studies combine multiple ablative procedures or utilize ablative techniques as an adjunct to surgical resection or chemotherapy. Studies also include patients with a broad range of tumor size and etiology. As a result, it is sometimes difficult to draw specific conclusions regarding the efficacy of an ablative technique. Careful selection of candidates for each treatment option and expert application of these treatments are required to achieve best outcomes.

Laser Ablation
Laser ablation (LA), also known as laser coagulation therapy, laser interstitial tumor therapy (LITT), and laser interstitial photocoagulation, refers to thermal tissue destruction by conversion of absorbed light (usually infrared) into heat. The infrared energy penetrates tissue directly for a distance of 12 to 15 millimeters (mm) and temperatures above 60 degrees centigrade cause rapid coagulative necrosis and instant cell death. The most widely used device for LA techniques is the Nd: YAG (neodymium: yttrium- aluminum-garnet) laser (Flexilase; Living Technology, Glasgow, Scotland) with a wavelength of 1064 nanometers (nm). Additionally, more compact diode lasers with shorter wavelengths (800 nm to 980 nm) have been utilized. A range of imaging modalities have been used to guide percutaneous LA techniques including ultrasound-guided needle placement, and magnetic resonance (MR) with contrast. However, the use of this technique is limited by the amount of local experience and resource/machine availability.

Laser ablation has been primarily studied in the treatment of brain, spine, and prostate tumors, but has been cleared by the U.S. Food and Drug Administration (FDA) for any soft tissue tumor (FDA, 2010). Percutaneous LA has received increasing attention for the treatment of a variety of primary and secondary malignant tumors, including hepatic tumors. However, of all the ablation techniques for hepatic tumors, LA has the least amount of published literature. Laser ablation is mainly applied in Europe and the majority of data reported on laser ablative techniques came from Italy, Germany, and the United Kingdom (Gough-Palmer & Gedroyc, 2008). The majority of long-term survival data was reported on hepatic metastases and varied in the literature; virtually no data has been published for HCC LA.
Five-year survival rates of 26% and median survival rates of 27 to 39 months have been reported. Pacella and colleagues reported on a series of 148 patients (144 biopsy proven HCC) treated with 239 laser ablative sessions. The authors quoted long-term survival rates of 89% at one year, 52% at three years, and 27% at five years and an overall complete lesion ablation rate of 82%. Pul et al reported on 87 consecutive patients with 180 liver metastases from CRC who underwent laser ablation with MR thermometry in 170 sessions. Median survival time was 54 months and survival rates were 95.7% at one year, 86.2% at two years, 72.4% at three years, 50.1% at four years, and 33.4% at five years. Although, these results appeared encouraging, direct comparison with other ablative therapies (e.g., RFA) in prospective clinical trials are needed to show definitively which modality is superior.

Selection criteria in these studies varied on the technique used and the facilities available but were in general, similar to other locally ablative techniques such as RFA and MWA. Many of the studies were performed on multiple tumor types, making it difficult to evaluate the efficacy of laser ablation. The range of imaging modalities used at follow-up combined with a variety of definitions of treatment success, made comparison of the data difficult.

The NCCN guidelines for HCC do not include or discuss LA as a technique of locoregional ablation. While laser ablation appears safe, evaluation of its effectiveness is limited by lack of good comparative trials and hampered by constantly changing technologies. The clinical efficacy of laser ablation has not been established at this time. Further data from randomized studies evaluating the impact of LA on survival, quality of life, and cost-effectiveness for both primary and secondary liver tumors is required.

Unresectable Hepatocellular Carcinoma Tumors in the Transplant Setting
As noted earlier, liver transplantation is the only curative alternative for unresectable HCC. Locoregional therapies (e.g., ablation, TACE) have been explored in various settings including as a technique to prevent tumor progression in patients on the liver transplant waiting list, downstaging tumors such that the patient will be considered a better candidate for liver transplantation, and decreasing the incidence of post-transplant recurrence in patients with larger (T3) tumors. All of these indications are in part related to the United Network for Organ Sharing (UNOS) liver allocation policy, which prioritizes patients for receiving donor livers. The UNOS policy recognized pretransplant locoregional therapies including “chemoembolization of lesion, radiofrequency, cryo, or chemical ablation of the lesion,” as a component of patient management during the waiting period.

In 2002, UNOS introduced a new liver allocation system, model for end stage liver disease (referred to as MELD) for adult patients awaiting liver transplant. The MELD score is a continuous disease severity scale incorporating bilirubin, prothrombin time (i.e., international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 (less ill) to 40 (gravely ill). Aside from those in fulminant liver failure, donor livers are prioritized to those with the highest MELD number. This scale accurately predicts the risk of dying from liver disease except for those with HCC, who often have low MELD scores since bilirubin, INR, and creatinine levels are near normal. Therefore, patients with HCC are assigned additional allocation points according to the size and number (T stage) of tumor nodules as follows:

- T1: One nodule, 1.9 cm or smaller
- T2: One nodule between 2.0 to 5.0 cm, or two or three nodules each smaller than 3.0 cm
- T3: One nodule larger than 5.0 cm, or two or three nodules with at least one larger than 3.0 cm

In considering how to allocate the scarce donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions are at high risk of
post-transplant recurrence, and are generally not considered transplant candidates. Patients with T2 tumors have an increased risk of dying while on the waiting list compared to those with T1 lesions and an acceptable risk of post-transplant tumor recurrence. Therefore, UNOS criteria prioritize T2 HCC by allocating additional point’s equivalent to a MELD score predicting a 15% probability of death within three months. This definition of T2 lesions is often referred to as the “Milan criteria,” in reference to a key study reported by Mazzaferro et al that examined the recurrence rate of HCC according to the size of the initial tumor.53 Note that liver transplantation for those with T3 HCC is not prohibited, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting transplantation are reassessed at three-month intervals. Those whose tumors have progressed and are no longer T2 tumors will lose the additional allocation points.

Therefore, the UNOS allocation system provides strong incentives to use locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list. Promfet et al report of a national conference on liver allocation in patients with HCC in the U.S. addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early stage HCC on the transplant waiting list in the U.S..54 At the completion of the meeting, there was a general consensus for the development of a calculated continuous HCC priority score for ranking HCC candidates on the list that would incorporate the calculated MELD score, alpha-fetoprotein, tumor size, and rate of tumor growth and that only candidates with at least stage T2 tumors would receive additional HCC priority points.

**Locoregional Therapies as a Bridge to Transplant**

Several studies have reported dropout rates of wait-listed patients treated with locoregional therapy. However, lacking controlled data, it is difficult to assess contributions of locoregional therapy to time on the waiting list. In addition, in 2002, as discussed above, UNOS revised its liver allocation policy, such that wait times for patients with HCC meeting the “Milan criteria” have now declined.52

The majority of the literature has focused either on TACE or a variety of locoregional therapies. Given these limitations the following case series have been reported: Graziadei et al reported on 48 patients with HCC awaiting transplantation; all underwent TACE every six to eight weeks until a complete response or a donor organ became available.55 No patients were removed from the list due to tumor progression and mean waiting time was 178 (+/- 105) days. Maddala et al studied the dropout rates of 54 patients receiving TACE while awaiting transplantation.56 During a median waiting time of 211 days (range: 28 to 1,099 days), the dropout rate was 15%. Obed et al reported on 20 patients with non-progression of lesions after TACE who had liver transplantation; median survival in this group was 92.3 months.57

Fisher et al reported on 33 patients who received multimodality ablation therapy, consisting primarily of RFA or TACE.58 Five patients (12%) were removed from the waiting list after waits of five to 14 months. In this protocol, patients with tumors larger than 5 cm were not considered transplant candidates until the tumor was completely ablated using TACE, RFA, or another technique. Yamashiki et al reported on 288 patients given various ablative therapies; the dropout rate due to tumor progression at one and three years was 6.25 and 23% respectively.59 Tumors larger than 3 cm affected the dropout rate due to tumor progression. Mazzaferro et al reported on 50 patients with HCC who underwent RFA while awaiting transplantation; no patient had to be removed from the waiting list due to tumor progression. The dropout rate due to tumor progression over a mean wait time of 9.5 months.60 The median tumor size was 3 cm, and 80% of patients met the Milan criteria. Similarly, Lu et al reported on 52 patients who underwent RFA as a bridge to transplantation, 42 of whom met the Milan criteria.61 After a mean of 12 months, 5.8% had dropped off the waiting list due to tumor progression.

In a 2008 paper, Belghiti et al reviewed the literature reporting efficacy of local management...
approaches including resection, TACE, RFA, and no treatment. They concluded RFA can induce complete necrosis in the majority of small tumors (less than 2.5 cm) and there was no data demonstrating that the treatment reduced the rate of drop out before transplantation or improved survival after transplant. None of the studies included data from U.S. centers for patients listed after adoption of the Milan criteria. Porrett et al retrospectively compared 31 patients treated with RFA with 33 untreated controls. Only 20% of treated tumors demonstrated complete ablation (necrosis) as defined by histologic examination of the entire lesion. Only 55% of lesions with histologic viable tumor was detected by MRI after pretransplant therapy. After 36 months of follow-up, there was no difference between the treated and untreated groups in overall survival (84 versus 91%), disease-free survival (74% versus 85%), cancer recurrence (23% versus 12%), or mortality from cancer recurrence (57% versus 25% - all respectively) (p > 0.1). The authors concluded viable tumor frequently persisted after pretransplant locoregional therapy and neoadjuvant treatment did not appear to improve post-transplant outcomes in the current MELD era.

The UNOS policy on allocation of livers indicated candidates whose tumors have been ablated after meeting the criteria for additional MELD/PELD (PELD calculator for persons under age 12 years) points will continue to receive additional points (equivalent to a 10% increase in mortality) every three months without review, even if the estimated size of residual viable tumor falls below stage T2 criteria. The policy also noted candidates may be removed from the listing if they are determined to be unsuitable for transplantation based on progression of HCC.

**Locoregional Therapies to Downstage Hepatocellular Carcinoma Prior to Transplant**

Yao et al analyzed longer-term outcome data on HCC downstaging in a cohort of 61 patients with tumor stage exceeding T2 criteria enrolled between June 2002 and January 2007. Eligibility criteria for downstaging included: 1) one lesion larger than 5 cm and up to 8 cm; 2) two to three lesions with at least one lesion larger than 3 cm and not exceeding 5 cm, with total tumor diameter up to 8 cm; or 3) four to five lesions with none larger than 3 cm, with total tumor diameter up to 8 cm. Transcatheter arterial chemoablation and laparoscopic RFA (LRFA) either alone or in combination were the main methods used: 11 patients received LRFA alone, 14 received TACE and LRFA, and nine received TACE and percutaneous RFA. A minimum observation period of three months after downstaging was required before liver transplant.

Tumor downstaging was successful in 43 patients (70.5%). Thirty-five patients (57.4%) received liver transplant, including two with live-donor liver transplantation. Treatment failure was observed in 18 patients (29.5%), primarily due to tumor progression. In the explant of 35 patients who underwent transplant, 13 had complete tumor necrosis, 17 met T2 criteria, and five exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival analysis at one and four years after downstaging was 87.5% and 69.3%, respectively. The one-year and four-year post-transplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median post-transplantation follow-up of 25 months. The only factor predicting treatment failure was pretreatment alpha-fetoprotein greater than 1,000 ng/mL. From this small series, the authors concluded successful downstaging can be achieved with excellent post-transplant outcomes.

Lewandowski et al compared radioembolization with chemoembolization (TACE) in the efficacy of downstaging 86 patients with HCC from stage T3 to T2. Patients were treated with either 90-yttrium microspheres (n = 43) or TACE (n = 43). Median tumor size was similar between the two treatment groups (5.7 and 5.6 cm, for TACE versus radioembolization, respectively). Partial response rates were 61% versus 37% for radioembolization versus TACE, respectively with downstaging from T3 to T2 in 58% of patients treated with radioembolization versus 31% with TACE (p < 0.05).

As part of a national conference involving transplant physicians, workgroups were formed to discuss the policy of assigning increased priority for candidates with stage T2 HCC on the transplant list in the U.S. The workgroup assigned to the role of downstaging in transplant
candidates with HCC noted inconsistent outcomes reported in the literature and proposed a
definition of downstaging that would include TACE and various ablative techniques but not
resection. Promfet et al noted that only two regions have adopted a downstaging protocol.54

The results and efficacy of downstaging with TACE to achieve a reduction in tumor burden to a
T2 lesion remain controversial. There are retrospective data showing the ability to downstage
patients with TACE; however, there is no randomized evidence that tumor downstaging prior to
liver transplant confers a survival advantage.

Locoregional Therapies to Reduce Risk of Recurrence of T3 Tumors
Published literature by Pomfret et al reflects an ongoing discussion as to whether the UNOS
allocation criteria should expand to include patients with larger tumors.54 An additional indication
for locoregional therapies focused on their use in patients with T3 tumors, specifically to reduce
the incidence of recurrence post-transplant. If the incidence of recurrence can be reduced,
then Yao et al, Yao et al, Fernandez et al, Merli et al, and Sauer et al reported that advocates
have argued the UNOS allocation criteria should not discriminate against patients with larger
tumors.67,68,69,70,71 Some patients with T3 lesions apparently are cured with liver transplant, although
most experience recurrent tumor. For example, in the seminal 1996 study by Mazzaferro et al, the
four-year recurrence-free survival was 92% in those who met the Milan criteria (T2 lesion)
compared to 59% in those who did not; Sauer et al reported additional studies confirmed this
difference in recurrence-free survival rate.53,71 However, other institutions have reported similar
outcomes with expanded criteria. For example, Yao and colleagues at University of California at
San Francisco (UCSF) reported similar recurrence-free survival after transplant in patients with T2
and a subset of those with T3 tumors. This T3 subset was defined as a single lesion less than 6.5 cm
or less than three lesions with none greater than 3 cm and with a sum of tumor diameters less
than 8 cm. These expanded criteria are known as the UCSF criteria reported by Yao et al.67

The question is whether locoregional therapies (including both RFA and TACE) may decrease the
recurrence rate in patients meeting the UCSF criteria. Yao and colleagues published a detailed
analysis of 121 patients with HCC who underwent transplantation.67 Seventy-eight patients (64%)
had T2 lesions, while an additional 27 patients (22.3%) met the expanded UCSF criteria, termed
T3A lesions. The rest had T1, T3B, or T4 lesions. Individual patients received a variety of
preoperative locoregional therapies, including TACE or ablative therapies, such as PEI, RFA, or
combined therapies. A total of 38.7% of patients did not receive preoperative locoregional
therapy. The one- and five-year recurrence-free survival was similar in those with T2 and T3A
lesions, while the corresponding recurrence-free rates were significantly lower for those with T3B
and T4 lesions.

The authors also compared recurrence-free survival of those who did and did not receive
locoregional therapy. For those with T2 lesions, the recurrence rates were similar whether or not
the patient received locoregional therapy. However, for T3 lesions (including both T3A and T3B),
the five-year recurrence-free survival was 85.9% for those who received locoregional therapy
compared to 51.4% in those who did not. When the data for T2 and T3 lesions were grouped
together, the five-year recurrence-free survival was 93.8% for those who received locoregional
therapy compared to 80.6% in those who did not. The authors concluded preoperative
locoregional therapy may confer a survival benefit in those with T2 or T3 lesions. The authors
noted several limitations to the study, including the retrospective nature of the data and the
marginal statistical significance of the improved survival given the small numbers of patients in
each subgroup. For example, only 19 patients were in the T3A (i.e., UCSF expanded criteria)
subgroup. In addition, no protocol specified which type of locoregional therapy to offer different
patients. These therapies are only offered to those patients with a adequate liver reserve; such
patients may have an improved outcome regardless of the preoperative management.

Summary of Evidence
For individuals who have an unresectable primary or metastatic tumor (e.g., breast, hepatic
[primary or metastatic], pulmonary, renal) who receive MWA, the evidence includes case series,
observational studies, cohort studies, RCTs, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related mortality and morbidity. Available studies have shown that MWA results in a wide range of complete tissue ablation (50%-100%) depending on tumor size, with complete ablation common and nearing 100% with smaller tumors (e.g., ≤3 cm). Tumor recurrence rates at ablated sites are very low. However, tumor recurrence at nonablated sites is common and may correlate with disease state (e.g., in hepatocellular carcinoma). Intraoperative and postoperative minor and major complications are low, especially when tumors are smaller and accessible. Patient selection criteria and rationale for using MWA instead of other established techniques (e.g., surgical resection, radiofrequency ablation) are needed. The evidence is insufficient to determine the effects of the technology on health outcomes. While some earlier studies found MWA required more treatment sessions to achieve adequate ablation, more recent studies using newer MWA technology that deliver larger ablation zones with cooled-shaft antennas have demonstrated shorter ablation times and fewer complications.

In conclusion, although comparisons among the various locoregional therapies are difficult due to factors such as interstudy patient and treatment heterogeneity, differences in patient management protocols and multimodality treatment protocols, the body of data illustrates the likely overall benefit of certain locoregional therapies for specific patient populations.

Supplemental Information

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2016 Input

In response to requests Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 1 academic medical center in 2016. This number of responses was less than optimal. Input overall was mixed. There was some support for the medical necessity of microwave ablation (MWA) in each category, with some reviewers indicating that it was standard of care for certain tumors. However, there were no indications for which all 3 reviewers agreed that MWA should be medically necessary.

2011 Input

In response to requests Blue Cross Blue Shield Association, input was received from 2 physician specialty societies (3 reviews) and 4 academic medical centers (6 reviews). Eight reviewers considered MWA investigational to treat primary tumors such as hepatocellular carcinoma, benign and malignant renal tumors, lung tumors, adrenal tumors, or cholangiocarcinoma. The reviewers noted insufficient evidence and a need for further studies on MWA. However, 1 reviewer indicated MWA for primary tumors, including, but not limited to hepatocellular carcinoma, benign and malignant renal tumors, lung tumors, adrenal tumors and cholangiocarcinoma, may be considered a treatment option, and another reviewer indicated that MWA for renal tumors may be considered a treatment option.

Four reviewers considered MWA investigational to treat liver metastases, and 2 reviewers indicated MWA for liver metastases may be considered a treatment option. One reviewer noted MWA may be appropriate for tumors not amenable to radiofrequency ablation or other local treatments. This reviewer also suggested MWA may be more appropriate for tumors located near large blood vessels.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines on hepatobiliary cancers (v.2.2018) list microwave ablation (MWA) (along with radiofrequency ablation, cryoablation, and...
percutaneous alcohol injection) as a treatment option for hepatocellular carcinoma (HCC) tumors in patients who are not candidates for potential curative treatments (e.g., resection and transplantation) and do not have large-volume extrahepatic disease. Ablation should only be considered when tumors are accessible by percutaneous, laparoscopic, or open approaches. The guidelines indicate “ablative therapies are most effective for [HCC] tumors less than 3 cm...”. HCC tumors between 3 and 5 cm may also be treated with ablation to prolong survival when used in combination with arterial embolization. Additionally, the tumor location must be accessible to permit ablation of the tumor and tumor margins without ablating major vessels, bile ducts, the diaphragm, or other abdominal organs. However, only 2 randomized controlled trials were cited in the guidelines to support recommendations for MWA.

The Network guidelines on neuroendocrine tumors (v.2.2018) do not mention MWA. Guidelines state that: “Cytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoaablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended.”

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (2016) updated its guidance on MWA for treatment of metastases in the liver. The revised guidance indicated that: “Current evidence on microwave ablation for treating liver metastases raises no major safety concerns and the evidence on efficacy is adequate in terms of tumor ablation.”

The Institute (2007) also published guidance on MWA for HCC. This guidance indicated: “Current evidence on the safety and efficacy of microwave ablation of hepatocellular carcinoma appears adequate to support the use of this procedure...” The guidance also stated there are no major concerns about the efficacy of MWA, but noted that limited, long-term survival data are available.

**American College of Chest Physicians**

The American College of Chest Physicians’ 2013 evidence-based guidelines on the treatment of non-small-cell lung cancer noted that the role of ablative therapies in the treatment of high-risk patients with stage I non-small-cell lung cancer is evolving. The guidelines deal mostly with radiofrequency ablation.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in August 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**References**

44. Doyle MBM, Lineham DC. (2009). Thermal Ablation of Liver Tumors by Radiofrequency, Microwave, and Laser Therapy, in Malignant Liver Tumors: Current and Emerging

**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**
- History and physical, and/or consultation reports and progress notes including:
  - Clinical indications/justification of procedure
  - Eastern Cooperative Oncology Group functional status (if applicable)
  - Previous treatment(s), duration, and response(s)
  - Treatment plan
  - Tumor type and description (i.e., resectable or unresectable, primary or metastatic,
tumor burden [e.g., liver dominant])

- Pertinent radiological imaging results (i.e., abdominal CT and/or MRI and/or PET)
- Pathology report including tumor node metastasis (TNM) classification
- Current serum chemistry, liver function tests, and tumor marker results

**Post Service**

- Results/reports of tests performed
- Procedure report(s)

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.